General

Guideline Title

Comparison of Oncotype DX with multi-gene profiling assays (e.g., MammaPrint, PAM50) and other tests (e.g., *Adjuvant! Online*, Ki-67 and IHC4) in early-stage breast cancer.

Bibliographic Source(s)

Chang M, Ismaila N, Kamel-Reid S, Rutherford M, Hart J, Bedard P, Trudeau M, Eisen A, Molecular Oncology Advisory Committee. Comparison of Oncotype DX with multi-gene profiling assays (e.g., MammaPrint, PAM50) and other tests (e.g., Adjuvant! Online, Ki-67 and IHC4) in early-stage breast cancer. Toronto (ON): Cancer Care Ontario (CCO); 2013 Nov 20. 39 p. (Recommendation report; no. MOAC-2). [39 references]

Guideline Status

This is the current release of the guideline.

The RECOMMENDATION report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Recommendation 1

In cases of breast carcinoma where Oncotype DX is indicated for clinical prognosis and treatment decisions, other assays should not currently be considered equivalent with respect to data generated or risk stratification.

Recommendation 2

In cases where it is unclear whether or not Oncotype DX is indicated for clinical prognosis and treatment decisions, *Adjuvant! Online* may be used as a no-cost method to estimate the tumour recurrence risk. These assays should not be considered equivalent to Oncotype DX if the latter is indicated (see Recommendation 1).

Recommendation 3

Given the preliminary status of much of the available evidence, periodic reassessment of published and ongoing trials is recommended. New

evidence supporting molecular profiling tests should be reviewed at least semi-annually.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Early-stage breast cancer

Guideline Category

Risk Assessment

Technology Assessment

Clinical Specialty

Medical Genetics

Obstetrics and Gynecology

Oncology

Intended Users

Other

Patients

Physicians

Guideline Objective(s)

To determine if testing that is sent out of country can be patriated by equally effective alternate tests that are now commercially available in Ontario

Note: This report is not intended to provide recommendations on appropriate indications for the use of Oncotype DX or any other test. It is assumed in the report that the indications for the use of these tests are understood by the clinicians using them.

Target Population

Patients with early-stage breast cancer

Interventions and Practices Considered

1. Oncotype DX
2. *Adjuvant! Online*
3. Periodic reassessment of published and ongoing clinical trials

Major Outcomes Considered

- Validity and utility of multi-gene profiling assays
- Comparison of risk scores
- Reclassification of recurrence score (RS)
- Distant recurrence (DR)
- Relapse prediction
- Risk estimations
- Risk reclassification
- 10-year relapse risk
- Risk allocation
- Time to first DR

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This evidentiary base was developed using a planned three-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing guidelines that may be suitable for adaptation.
2. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews are identified that address the research questions and are of reasonable quality, then those systematic reviews would form the core of the evidentiary base.
3. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

Guideline Review

Almost all Program in Evidence-based Care (PEBC) document projects begin with a search for existing guidelines that may be suitable for adaptation. The PEBC defines adaptation, in accordance with the ADAPTE Collaboration, as "the use and/or modification of (a) guideline(s) produced in one cultural and organizational setting for application in a different context". This includes a wide spectrum of potential activities from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with *de novo* recommendations development.

For this document, a search was conducted of the Inventory of Cancer Guidelines, the National Guidelines Clearinghouse and the Canadian Medical Association Journal (CMAJ) Infobase. In addition, the websites of several known high-quality guideline developers, including National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society for Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), National Health and Medical Research Council (Aus), and New Zealand Guidelines Group were searched. Only guidelines published after 1999 were considered.

Search for Existing Systematic Reviews

A systematic search was conducted in OVID MEDLINE (1996 through April 2013), EMBASE (1996 to 2013 week 15), the Cochrane library (Issue 2-4, April 2013), PubMed, San Antonio Breast Cancer Symposium (SABCS) (2010-2012), and ASCO conference proceedings (1999 to 2013). The keyword "Oncotype DX" or "21-gene assay" was used as the search term. Systematic reviews were included if:

1. They evaluated randomised or non-randomised control trials of patient with early-stage breast cancer that have been evaluated with Oncotype DX and any other test.

2. The literature search strategy for the existing systematic review is reproducible (i.e., reported) and appropriate.
3. The existing systematic review reported the sources searched as well as the dates that were searched.

Identified systematic reviews that meet the eligibility criteria would be assessed using the AMSTAR tool. The results of the AMSTAR assessment would be used to determine whether or not an existing review could be incorporated as part of the evidentiary base.

Any identified reviews that did not meet the criteria above, whose AMSTAR assessment indicated important deficiencies in quality, or that was otherwise not incorporated as part of the evidence base would be reported in the reference list, but not described or discussed further.

Primary Literature Systematic Review

Assuming that no existing systematic review was identified, or that identified reviews were incomplete in some fashion, a systematic review of the primary literature was also planned. This review would be reduced in scope, such as a reduction in subject areas covered, time frames covered, etc., based on the scope of incorporated existing reviews. The criteria described below are written assuming no existing reviews would be incorporated.

Literature Search Strategy

Details of the literature search strategy is included in Appendix 2 in the original guideline document.

Study Selection Criteria and Protocol

Articles were selected for inclusion in this systematic review of evidence if they were fully published reports or published abstracts of randomised or non-randomised control trials.

Inclusion Criteria

1. Study must have investigated Oncotype DX in comparison with any other test.
2. Study was a randomised controlled trial (RCT) or non-RCT that included a subgroup analysis based on biomarker status.
3. Cohort studies with an analysis of comparison of biomarker status.

Exclusion Criteria

1. Letters, comments or editorials
2. Single-arm studies
3. Non-systematic reviews
4. Non-English publications

A review of the titles and abstracts that resulted from the search was done independently by one of the reviewers. For those items that warranted full-text review, this reviewer reviewed each item independently. However, in cases where there was uncertainty in including a certain article, a second reviewer was asked to review.

Number of Source Documents

Fifteen full texts and 13 abstracts from 22 studies were eligible to be included in the primary literature systematic review. Four of these studies had duplicate publications, while one study had three publications. Data was extracted from the most recent publication. Details of the characteristics of the studies are included in Table 2 in the original guideline document.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the included studies was independently extracted by one reviewer. If more than one publication addressed the same study, only the most updated or recent versions of the data were reported in the result. All extracted data and information was audited by an independent auditor.

Quality assessment of individual studies could not be carried out because most of the studies included (65%) were in abstract form. Thus, there was limitation in the extraction of data necessary to assess the quality of the studies.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis would be conducted using the Review Manager software (RevMan 5) available from the Cochrane Collaboration. For time-to-event outcomes, hazard ratios (HR), rather than the number of events at a certain time point, would be the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, they would be derived from other information reported in the study, if possible, using the methods described by Parmar et al. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in RevMan software would be used.

Statistical heterogeneity would be calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Molecular Oncology Advisory Committee (MOAC) was been asked by the Ontario Ministry of Health to "develop evidence-based advice to inform system planning, new test development, access and quality assurance." The scope of the committee was to review current and emerging knowledge and to make recommendations on the optimal application of molecular testing for cancer risk, diagnosis, monitoring, prognosis, or prediction of response to treatment for the benefit of Ontarians and Ontario cancer patients. In order to make recommendations as part of clinical practice, the working group of the MOAC developed the evidentiary base upon which those recommendations are made.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Internal Review

Almost all Program in Evidence-based Care (PEBC) documents undergo internal review. With recommendation reports, this review is conducted by the Director of the PEBC. The Working Group is responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by retrospective and prospective studies.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate molecular profile testing and estimation of tumour recurrence risk in women with early stage breast cancer

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- Recommendation 1 is based on evidence directly comparing Oncotype DX with other assays. Most of the available evidence consists of studies presented as abstracts rather than peer-reviewed publications. There are other gene-expression profiling assays that have been recognized in the U.S., Canada, and/or Europe as having clinical validity for prognostication in breast cancer. For example, the MammaPrint 70-gene classifier is a U.S. Food and Drug Administration (FDA)-cleared prognostic test, and both MammaPrint and PAM50 are recognized as prognostic tests in Europe. The evidence supporting the use of these assays in their own right should be evaluated in clinical decision making; however, analysis of individual validation studies is outside the scope of this review.
- Oncotype DX is a test that guides decisions concerning chemotherapy in women with estrogen receptor (ER)-positive and node-negative breast cancer. It should not be considered a routine test to be sought for all women with ER-positive–node-negative disease. The actual decision to treat with cytotoxic agents depends on other clinical factors, including patient age, comorbidities, and the patient's own treatment preferences. The incorporation of additional data (e.g., Adjuvant! Online, other clinicopathologic features) also plays a role in informing this decision. Therefore, the decision to undergo Oncotype DX testing requires clinical judgment taking into account all of these factors. As more scientific evidence becomes more available to support the clinical utility of other assays, they may become more useful
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Nov 20

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Molecular Oncology Advisory Committee

Composition of Group That Authored the Guideline

Authors: M. Chang, N. Ismaila, S. Kamel-Reid, M. Rutherford, J. Hart, P. Bedard, M. Trudeau, A. Eisen

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, Molecular Oncology Advisory Committee (MOAC) members, and internal and external reviewers were asked to disclose potential conflicts of interest.

The authors, members, and reviewers reported that they had no conflicts of interest.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Comparison of Oncotype DX with multi-gene profiling assays (e.g., MammaPrint, PAM50) and other tests (e.g., Adjuvant! Online, Ki-67 and IHC4) in early-stage breast cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2013 Nov 20. 8 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available in PDF from the Cancer Care Ontario Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 10, 2014.

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